TEST PLAN FOR METHYLATED 2-IMIDAZOLIDINONE

January 21, 2005

OVERVIEW

The SOCMA Urea Resins Group (SURG) hereby submits a final test plan for 2-imidazolidinone, 4,5-dihydroxy-1,3-bis(hydroxymethyl)-, methylated (CAS No. 68411-81-4) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. Data on the methylated imidazolidinone were combined with data on the well, studied non-methylated analog (2-imidazolidinone, 4,5-dihydroxy-1,3-bis(hydroxymethyl)-)(CAS No. 1854-26-8) to fulfill most of the Screening Information Set (SIDS) endpoints. The non-methylated analog (CAS No. 1854-26-8) has already been reviewed as part of the OECD/SIDS program. Further comparisons were made between the methylated imidazolidinone and 2-imidazolidinone, 4,5-dihydroxy-1,3-bis(methoxymethyl)- (CAS No. 3001-61-4), for which various physical/chemical and environmental fate properties were estimated by modeling. The use of existing data from the non-methylated material and modeled data for the dimethylated material adequately fulfilled all SIDS endpoints except biodegradation and algal toxicity. Testing for these endpoints has been completed with the methylated material and is described in this final test plan.

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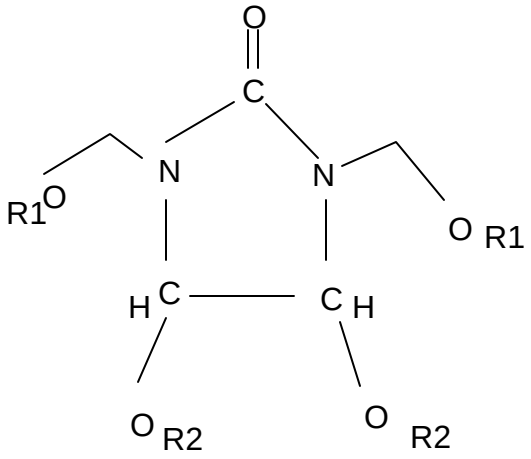
1. Information about the Panel

The SOCMA Urea Resins Group (SURG) is formed under the sponsorship of the Synthetic Organic Chemical Manufacturers Association (SOCMA). SURG consists of the following current or former manufacturers of methylated, substituted 2-imidazolidinone:

Hickson DanChem Corporation
Noveon, Inc.
OMNOVA Solutions Inc. (former manufacturer)

2. Identity of test substance and its analogs

The general molecular structure for the sponsored chemical and its analogs can be shown as follows"



Test Substance	Non-Methylated Analog	Dimethylated Analog
CAS # 68411-81-4	CAS # 1854-26-8	CAS #3001-61-4
R1, R2 = hydrogen and/or methyl	R1, R1 =hydrogen	R1 = methyl, R2 = hydrogen

The test substance, 2-imidazolidinone, 4,5-dihydroxy-1,3-bis(hydroxymethyl)-, methylated (CAS No. 68411-81-4), is methylated to an undetermined extent. Methylation occurs primarily such that one or both R1 groups are methyl groups instead of hydrogen atoms. It is possible that some R2 groups are also methyl instead of hydrogen.

The primary (data rich) analog is 2-imidazolidinone, 4,5-dihydroxy-1,3-bis(hydroxymethyl)- (CAS No. 1854-26-8). All R1s and R2s for this substance are hydrogen atoms. This substance has already been reviewed (SIAM 10) and been assigned a low priority for further work.

A second analog is 2-imidazolidinone, 4,5-dihydroxy-1,3-bis(methoxymethyl)- (CAS No. 3001-61-4). For this substance, the R1s are methyl groups and the R2s are hydrogen atoms. Very limited data exist for this substance. However, this analog is useful because chemical/physical and environmental fate properties can be estimated for this substance by modeling. The data obtained by modeling help to predict the effect methylation has on these properties.
For simplicity in referring to the test substance and the two analogs, they will be designated,

"Methylated imidazolidinone" = CAS No. 68411-81-4 (the test substance)

"Non-methylated imidazolidinone" = CAS No. 1854-26-8 (the data-rich analog)

"Dimethylated imidazolidinone" = CAS No. 3001-61-4 (the analog useful for comparative modeling)

3. Background Information on the Test Substance and surrogate

The test substance is manufactured by the reaction of glyoxal, urea and formaldehyde followed by methylation using methanol. The test substance is not isolated. It is produced and sold as an aqueous solution containing low levels (< 1.0%) of formaldehyde.

Both the test substance and the surrogates are substituted 4,5-dihydroxy-1,3-hydroxymethyl-2-imidazolidinones that are used in textile manufacture as industrial intermediates to produce easy care fabrics. They are applied to textile cloth and cured to crosslink with the cellulose molecules in the cloth, so that the finished textile cloth will have "memory" to retain crease or other desired shape. The methylated test substance contains lower residual levels of formaldehyde compared to the non-methylated analog. Residual formaldehyde in these products is released during processing, therefore minimizing any potential consumer exposure.

4. Test Plan

It is the intention of the SOCMA Urea Resins Group, which includes the manufacturers of "methylated imidazolidinone" (CAS No. 68411-81-4) to use information on this substance, combined with available studies on the related "non-methylated imidazolidinone" (CAS No. 1854-26-8) to fulfill the screening information data needs. An IUCLID data set summarizing the available studies (with Klimisch codes) for CAS No. 1854-26-8 existed (IUCLID, 2000), as well as a SIAR. CAS No. 1854-26-8 was reviewed at SIAM 10, and assigned "low priority for further work." The initial test plan and robust summaries were posted on the EPA website on February 26, 2002. A revised test plan and summaries were posted on August 28, 2003. That plan indicated that the methylated imidazolidinone (CAS No. 68411-81-4) would be tested for biodegradation and algal toxicity. This testing was recommended to allay concerns that the methylated imidazolidinone (CAS No. 68411-81-4) would degrade more slowly and be more toxic to algae than the non-methylated imidazolidinone (CAS No. 1854-26-8). Testing for the aforementioned endpoints has been completed, and the current test plan (and accompanying robust summary document) communicates their results (in addition to data previously submitted). The test substance used in conducting studies was the commercial product with the highest available concentration of CAS No. 68411-81-4 in solution at the time of testing. Testing

that has been performed fulfills all requirements of the HPV program; therefore this test plan and robust summary document are considered final.

4.1 Chemical/Physical Properties

Chemical and physical property data for the related "non-methylated imidazolidinone" (CAS No. 1854-26-8) are also shown in Table 1. Values for the two materials are comparable, demonstrating close resemblance in chemical physical properties.

Chemical/Physical Property data for CAS No. 68411-81-4 are reported in Table 1. A melting point of -39º C has been determined using OECD Guideline 102 "Melting Point/Melting Range" under good laboratory practices (Tognucci, 2001a)(Table 1). A boiling point of 118.5º C at 980 hPa has been determined using OECD Guide-line 103 "Boiling Point/Boiling Range" employing good laboratory practices (Tognucci, 2001b). A specific gravity of 1.30-1.31 @25°C is provided in the Material Safety Data Sheet from Noveon, Inc. (2001).

Table 1. Chemical/physical properties of substituted 2-imidazolidinones

Endpoint	Methylated imidazolidinone (CAS No. 68411-81-4)[1]	Dihydroxy imidazolidinone (CAS No. 1854-26-8)[2]
Melting point (° C)	-39	-35
Boiling point (° C)	118.5	106
Density	1.30- 1.31	1.36
Partition coefficient (log Kow)	-3.2	-2.2
Water solubility (g/l)	> 5000	Miscible
Vapor pressure	Similar to water	Similar to water

[1]The test substance had the following composition: ca. 84% CAS No. 68411-81-4; ca. 13% H_2O, and 0.18% formaldehyde (CAS No. 50-00-0)

[2] Data were obtained from IUCLID data set for CAS No. 1854-26-8, dated 04-FEB-2000.

A water solubility of > 5000 g/l at 20º C was determined using OECD Guide-line 105 "Water Solubility" (Tognucci, 2001d).

The vapor pressures of the neat test product or its analogs are not known. However, these materials are commercially available as aqueous concentrates, and therefore are likely to have vapor pressures similar to water (water vapor pressure = 23.79 mm Hg or 31.71 hPa @ 25 °C).

A Log Kow of -3.2 at 20º C has been calculated from the following equation (Tognucci, 2001c):

log Kow = log (n-octanol solubility/water solubility = (<3.25 g/l / >5000 g/l) = < -3.2

This equation used the value of >5000g/l water solubility previously determined, and the value of <3.25 g/l for the solubility in n-octanol. The n-octanol solubility of the test material was determined to be <3.25 g/l by adding 0.13-0.14 grams of test material to 40 ml n-octanol at room temperature and stirring. The result was incomplete dissolving and two phases.

The negative log Kow indicates a greater propensity for the methylated material to partition to water than organic solvents.

4.2 Environmental Fate Parameters

Modeling data discussed below suggest that the nonmethylated, methylated, and dimethylated 2-imidazolidinones will have similar environmental fate properties.

Environmental fate parameters for methylated 2-imidazolidinone (CAS No. 68411-81-4) were obtained using the EPIWIN Program by modeling the surrogates. The test substance itself cannot be modeled, because it does not have a precise, defined molecular structure. Both nonmethylated 2-imidazolidinone (CAS No.1854-26-8) and the dimethylated 2-imidazolidinone (CAS No. 3001-61-4), which have well defined molecular structures, can be modeled using EPIWIN. As discussed above, these surrogates have closely analogous molecular structures, which bracket the molecular structure of methylated 2-imidazolidinone. Therefore the modeled environmental fate parameters of the surrogates should correspond closely to estimated parameters for methylated 2-imidazolidinone. Inputs to the model for both the nonmethylated and dimethylated surrogates were only the CAS numbers (i.e., SMILES codes). No measured data were inputted, since the only measured data (such as melting point, boiling point, or other physical property values) available were obtained on commercial grade CAS No. 1854-26-8, which always contains water. Inputting data determined on the commercial aqueous concentrate is not appropriate, since the model pertains to the hypothetical 100% chemical substance.

The comparative modeled environmental fate parameters for nonmethylated 2-imidazolidinone and dimethylated 2-imidazolidinone are listed in Table 2.

Table 2. Environmental fate parameters for substituted 2-imidazolidinones*

Environmental Fate Parameter	Nonmethylated 2-imidazolidinone (CAS No. 1854-26-8)	Dimethylated 2-imidazolidinone (CAS No. 3001-61-4)
Photolysis Hydroxyl Rate Constant (cm3/molecule-sec)	73.195 E-12	94.5 E-12
Photolysis half-life (days)	0.146	0.113
Stability in Water	Qualitatively stable	Qualitatively stable
Henry's Law Constant (atm-m3/mole)	1.06E-12	1.09E-13
Level III Fugacity: Air	0.00133 %	5.66E-6 %
Water	42.8 %	45.3 %
Soil	57.1 %	54.6 %
Sediment	0.0638 %	0.0755 %

* The values in this table for the analogs are predictive of the methylated test material of interest (CAS No. 68411-81-4), which cannot be modeled because it does not possess a precisely defined molecular structure.

As can be seen from the table, the values for both nonmethylated and dimethylated materials in general have close similarity. It is reasonable to expect for methylated test substance that the hydroxyl rate constant will range from 73.2 to 94.5 E-12 cm^3/molecule-sec. Similarly, the photolysis half-life will be between 0.11-0.15 days. There is about a 10-fold difference in the two Henry's Law Constants, but assuming a value for methylated test material between the range of 1.09E-13 to 10.6E-12 would indicate that all three compounds would display a low tendency toward volatilization from water. Fugacity Level III modeling for both the nonmethylated and dimethylated materials shows close agreement for relative concentrations in air, water, soil and sediment compartments under equilibrium conditions. It is reasonable therefore to expect that the methylated substance will preferentially partition to water and soil. Although stability of the test substance in water has not been determined, the commercial form of the product is as an aqueous concentrate. From a practical standpoint, therefore, it is likely that the product does not hydrolyze readily at neutral pHs (at ambient temperatures).

4.3 Biodegradation

An OECD Test Guideline 301B (Modified Sturm Test) was recently conducted with 45 mg/l of Freerez ® MTH-68 Resin, which contained 76.34% of the methylated imidazolidinone (CAS No. 68411-81-4) (RCC Ltd., 2004a). Under the conditions of the study, the test material was not readily biodegradable. After 28 days, the material had degraded by 4.5% (compared to 86.9% for the positive reference material).

4.4 Ecotoxicity

Results of ecotoxicity studies with the non-methylated imidazolidinone are summarized in Table 3. ECOSAR modeling predicts that both the non-methylated imidazolidinone and the dimethylated imidazolidinone exhibit low toxicity. Actual studies indicate low toxicity to fish, Daphnia and bacteria, and moderate to moderately high toxicity to algae. Although the ECOSAR predictions appear high in relation to the other studies, the modeling indicates that the presence or absence of methylation on the 1 and 3 hydroxymethyl positions does not have a significant bearing on aquatic toxicity. Therefore, it is reasonable to conclude that methylated imidazolidinone possesses a similar, low degree of toxicity to fish and Daphnia as both non-methylated imidazolidinone and dimethylated imidazolidinone. Accordingly, no additional studies are recommended for these species.

Since results of the BASF test showed that the nonmethylated analog was fairly toxic to algae (EC_{50} = 36.9 mg/l), and ECOSAR modeling predicted a somewhat lower EC_{50} value for the dimethylated than the nonmethylated material, algal toxicity testing (OECD Guideline 201) for the methylated material (CAS No. 68411-81-4) was conducted. The toxicity of Freerez ® MTH-68 Resin (76.34% CAS No. 68411-81-4) to Scenedesmus subspicatus was tested according to OECD Test Guideline 201 (RCC Ltd., 2004b). For this test, the indices of toxicity were inhibition of biomass, growth rate, and cell number. The NOEC and EC_{50} value at 72 hours for the most sensitive endpoint (cell number) were 22 and 109 mg/l, respectively. The EC_{50} value for the methylated material (109 mg/l) is slightly higher that of the nonmethylated material (36.9 mg/l), suggesting that the toxicity of the methylated material to aquatic species is slightly less

than that of the nonmethylated material. This supports the use of data from the nonmethylated material to fill the fish and Daphnid toxicity endpoints for the methylated material.

Table 3. Ecotoxicity Studies for substituted 2-imidazolidinones*

Endpoint	Non-methylated imidazolidinone (CAS No. 1854-26-8)	Methylated imidazolidinone (CAS No. 68411-81-4)	Dimethylated imidazolidinone (CAS No. 3001-61-4)
Acute toxicity to fish (96 hr LC_{50}, mg/l)	2200[a] 3.6E+9[b]	-	1.9E+7[b]
Acute toxicity to Daphnia (48 hr LC_{50}, mg/l)	>500[c,d] 2.23E+9[b]	-	1.4E+9[b]
Chronic toxicity to Daphnia (21 day NOEC, mg/l)	≥ 100[e]	-	-
Toxicity to algae (EC_{50}, mg/l)	36.9[c,f] 28.4[c,h] 8.85E+8[b,h]	109 [g]	6.41E+6[b,h]
Bacteria (mg/l)	2200[c,i] > 1000[j] 1995[k]	-	-

* Data for the methylated test material of interest (CAS No. 68411-81-4) are not available for any endpoint except algal toxicity. CAS No. 68411-81-4 cannot be modeled because it does not possess a precisely defined molecular structure.

[a] BASF AG, 1990. Active ingredient: 40%

[b] EPIWIN/ECOSAR Program (v0.99f).

[c] BASF AG, 1988. Active ingredient: 40%

[d] Directive 84/449/EEC, C.2 "Acute Toxicity for Daphnia"

[e] BASF AG, 1999; EEC Guideline XI/681/86. Active ingredient: 70%

[f] 72 hours

[g] RCC Ltd. , 2004. Active ingredient: 76.34%

[h] 96 hours

[i] Growth Inhibition Test, DIN 38412/8. 17 hr EC50. Active ingredient: 40%

[j] BASF AG, 1996. OECD Guideline 209 "Activated Sludge, Respiration Inhibition Test". 30 min NOEC. Active ingredient: 74%

[k] BASF AG, 1980. Short term respiration test. Highest concentration of material tested with < 20 % inhibition in 30 min.

4.5 Human Health Data

Results of mammalian toxicity tests conducted on the non-methylated imidazolidinone are summarized in Table 4. These studies indicate that the material has a low potential for acute, repeated dose, reproductive or developmental toxicity. Based on the structural similarity of the methylated material with the non-methylated material, the methylated material is also expected to have a fairly low potential for acute, repeated dose, genetic, reproductive, or developmental toxicity.

Table 4. Mammalian Toxicity Data for substituted 2-imidazolidinones*

Endpoint	Non-methylated imidazolidinone (CAS No. 1854-26-8)	Reference
Acute oral (LD_{50}, mg/kg)[1]	> 2,880 (rat)[2] > 10,000 (rat)[2] > 10,000 (mouse)[2]	BASF AG, 1973 IRDC, 1981b IRDC, 1981a
Acute inhalation	LC_{50} > 3.1 mg/l (rat)[2] LC_{50} > 3.0 mg/l (mouse)[2] No mortality after 8 or 1 hr exposure to saturated atmosphere @ 20 or 150 °C (respectively)	IRDC, 1981d IRDC, 1981c BASFAG, 1973
Repeated oral dose toxicity (NOAEL, mg/kg/day) [1]	1,000 (rat, 90 day) 4,000 (rat, 14 day) ≥ 6,000 (mouse, 90 day)[2] ≥ 11,680 (mouse, 14 day)[2]	IRDC, 1983b IRDC, 1981f IRDC, 1983a IRDC, 1981e
In vitro genetic toxicity (Ames)	TA97, TA98, TA 1535, TA1537, and TA102 -negative TA100 - equivocal	Zeiger et al., 1987 CCR, 1992; NTP, 1984 NTP, 1984; Zeiger et al., 1987
In vivo genetic toxicity	Mouse micronucleus at 2000 mg/kg - negative Sex linked recessive lethal at 60000 ppm in Drosophila - positive Reciprocal translocation at 50000 ppm in Drosophila - negative	Biopharm, 1995 Foureman et al., 1994 Foureman et al., 1994
Reproductive toxicity[3] (NOAEL, mg/kg) [1]	3,000 (rat) ≥ 6,000 (mouse)[2]	IRDC, 1983b IRDC, 1983a
Developmental toxicity (NOAEL, mg/kg) [1]	≥ 640 (rat)[2]	HMR, 1998

* Data for the methylated test material of interest (CAS No. 68411-81-4) and dimethylated imidazolidinone (CAS No. 3001-61-4) are not available

[1] Values refer to 100% test material

[2] Highest dose used

[3] Examination of reproductive organs from 90-day study

4.5.1 Acute Toxicity

Acute toxicity testing has not been conducted for the methylated imidazolidinone. Two acute oral studies for the rat and one for the mouse have been performed and summarized for the nonmethylated imidazolidinone. LD_{50} values ranged from >2,880 to >10,000 mg/kg. In mice receiving 2880 mg/kg by i.p. injection, the only symptoms observed were dyspnea and atony. Macroscopic inspection showed no pathological findings (BASF AG, 1973).

At ambient temperature, inhalation exposure for 8 hr to an atmosphere highly enriched in vapors from a 45 % aqueous solution (Fixapret CPN) caused no lethality, but caused dyspnea and irritation of mucous membranes (BASF AG, 1973). Vapors generated at 150° C produced severe irritation and dyspnea and were lethal to rats within a few hours (BASF AG, 1973). Spot-like hyperemia and edema of the lung were prominent, while hydrothorax was seen in isolated cases. It is assumed that decomposition products arising at temperatures greater than 40° C induced these serious effects (SIAR for CAS No. 1854-26-8; reviewed at SIAM 10).

Based on the structural similarity of the methylated material (CAS No. 68411-81-4) with the non-methylated material (CAS No. 1854-26-8), it is likely that the methylated material would also have fairly low acute oral and inhalation toxicity.

4.5.2 Repeated Dose Toxicity

No repeated dose studies have been identified for the methylated imidazolidinone (CAS No. 68411-81-4). Repeated dose studies are available in the rat and mouse for the related non-methylated imidazolidinone (CAS No. 1854-26-8)(Table 4). Fourteen-day oral (gavage) studies in rats and mice were conducted at doses ranging from 256 to 11,600 mg/kg/day (IRDC, 1983a,b). No test-related toxicologically significant macroscopic lesions or abnormalities were observed in rats or mice treated with any dose (with the exception of a moderately inflammatory bilateral reaction in the nasal passages of rats treated with 11,600 mg/kg).

Ninety-day oral (gavage) studies have been run in both the rat and the mouse for the non-methylated analog (CAS No. 1854-26-8)(Table 4) (IRDC, 1983a,b). Dose levels were 1000, 3000 and 6000 mg/kg/day of a material containing 41.4% CAS No. 1854-26-8. Pharmacotoxic signs noted for male and female rats in the 3000 and 6000 mg/kg/day dosage level groups including discoloration of the fur, soft stool, hypoactivity, decreased grasping reflex, ataxia, and decreased temperature of extremities. No deaths were reported and no toxicologically significant organ weight changes were observed. On postmortum examination, mild to moderate mineralization was observed in the heart and testes of two male rats, and multiple yellowish linear macroscopic lesions were observed in the right testis of one male rat treated with 6000 mg/kg/day.

In the 90-day mouse study, females of all dose groups and males at 1000 and 6000 mg/kg/day dose groups showed increased weight gains compared to controls (not toxicologically significant). The 6000 mg/kg/day group and controls showed no microscopically visible changes (the animals of the

1000 and 3000 mg/kg/day doses were not examined). One death occurred in the 3000 mg/kg male dose group at week three that was not considered treatment related.

The above studies are indicative of generally low repeated dose toxicity of non-methylated imidazolidinone (CAS No. 1854-26-8), even when adjusting the effective dose downward in the 90-day studies to reflect the 41.4% concentration of active ingredient. Based on the close structural similarity of non-methylated and methylated imidazolidinones, it is reasonable to conclude that the repeated dose toxicity of the methylated material (CAS No. 68411-81-4) would not differ significantly from that of the non-methylated material.

4.5.3 Genetic Toxicity

No genotoxicity studies have been identified for methylated imidazolidinone (CAS No. 68411-81-4). Three Ames tests are reported and summarized for non-methylated imidazolidinone (CAS No. 1854-26-8) (Zeiger et al., 1987; CCR, 1992; NTP, 1984). The tests show that non-methylated analog was negative in Salmonella strains TA1535, TA1537, and TA102 in the presence and absence of metabolic activation. However, results of the study by Zeiger et al., 1984 (which was conducted in two different laboratories) are equivocal for strains TA98 and TA100. In the presence of S-9, approximately 50% of tests in strain TA100 were questionable in one laboratory (with test material in DMSO) and all tests were positive in the other laboratory (with test material in water). Weakly positive or questionable results were found in strain TA98 in the presence or absence of S-9 in the same laboratory that found positive results in strain TA100 (material was in water). One out of five tests in the other laboratory with strain TA98 in the presence of S-9 (and test material in DMSO) showed a weak response. Because the tests with the two solvents were performed in different laboratories, it is difficult to discern whether the variable results were due to the tests being conducted in different laboratories or the use of different solvents.

Three *in vivo* genetic toxicity studies have been conducted in Drosophila melanogaster [two sex linked recessive lethal (SLR) and one reciprocal translocation)] with non-methylated imidazolidinone (Foureman et al., 1994). At a very high concentration of 60000 ppm (either orally or by i.p. injection), the test material induced a four-fold increase in sex-linked recessive lethal events. However, oral administration of a similar concentration (50000 ppm) did not lead to an increase in reciprocal translocations. Because the only concentration used in the sex-linked Drosophila study was very high, it is not known whether these effects occur at lower, more realistic exposure concentrations. Furthermore, due to study deficiencies, the sex-linked Drosophila study was assigned a reliability rating of 4. The Ames study is considered to be a more reliable test for assessing genotoxic potential of CAS No. 1854-26-8.

A mouse micronucleus study conducted on CAS No. 1854-26-8 under OECD Guideline 474, (using good laboratory practices) indicated that the test material did not increase the frequency of micronuclei at 2000 mg/kg (Biopharm, 1995).

The above studies are indicative of low potential for non-methylated imidazolidinone (CAS No. 1854-26-8) to produce genotoxicity. Only high doses of the material (generally 3333 mg/plate or higher) were shown to be mutagenic in some strains in the presence of S-9. Based on the close

structural similarity of non-methylated and methylated imidazolidinones, the in vitro genetic toxicity profile of the methylated material (CAS No. 68411-81-4) is not expected to differ significantly from that of the non-methylated material. Also, because the material is largely excreted unchanged in the urine upon oral administration and is not absorbed well from the skin (see Toxicokinetics below), the potential for DNA-reactive metabolites to be formed after in vivo exposure is low. Therefore, no additional in vitro testing is planned.

4.5.4 Reproductive Toxicity

No reproductive toxicity study has been identified for methylated imidazolidinone (CAS No. 68411-81-4). However, ninety-day oral (gavage) toxicity studies (that included examination of the reproductive organs of both sexes) on a material containing 41.4% of the non-methylated analog (CAS No. 1854-26-8) have been conducted in rats and mice (IRDC, 1983a,b). Microscopic inspection of these organs (including testes, epididymis, prostate, preputial gland/uterus, ovaries, clitoral gland) gave no indication of morphological abnormalities. No histopathological changes were observed up to 3000 mg/kg/day in male rats and up to 6000 mg/kg/day in female rats. No changes were seen up to 6000 mg/kg/day in both genders of mice. These studies are predictive of low reproductive toxicity for the methylated imidazolidinone. No additional studies are planned for this endpoint.

4.5.5 Developmental Toxicity

No developmental toxicity study has been identified for methylated imidazolidinone (CAS No. 68411-81-4). Teratogenicity testing has been conducted for non-methylated imidazolidinone (CAS No. 1854-26-8) in pregnant Wistar rats, following OECD Guideline 414 (HMR, 1998) (Table 4). No compound- related effects were observed at doses up to 1000 mg/kg. Since the test substance was 61.4% CAS No. 1854-26-8 in water, a NOAEL of 640 mg/kg was determined for both maternal toxicity and teratogenicity. Based on the structural similarity of the methylated imidazolidinone to the non-methylated material, this study should be predictive of developmental toxicity for methylated imidazolidinone. Therefore, no further testing is planned.

4.5.6 Other

4.5.6.1 Skin and eye irritation

No skin and eye irritation studies have been identified for methylated imidazolidinone (CAS No. 68411-81-4). Irritation studies are available for non-methylated imidazolidinone (CAS No. 1854-26-8). One skin irritation study (BASF AG, 1973) using the rabbit showed no irritation, and a secondary reference (Marhold [1972] in Czech) cited in RTECs indicated severe irritation. One eye irritation study using rabbits showed no irritation (BASF AG, 1973), whereas the same secondary RTECs Czech reference noted above indicated mild irritation. The BASF study is identified as the critical, valid study for this endpoint. Therefore, it is concluded that CAS No. 1854-26-8 is not highly irritating to the skin and eye. Based on the structural similarities between the methylated and nonmethylated material, strong skin and eye irritation is not likely to be associated with the methylated imidazolidinone (CAS No. 68411-81-4).

4.5.6.2 Sensitization

Human experience data with methylated imidazolidinone (CAS No. 68411-81-4) is limited. However, none of the sponsors identified any reports of skin sensitization in people who work with this material. Several cases of skin sensitization, dermatitis or eczema have been reported in humans who have contacted resin-treated textiles (Malten, 1964; Andersen and Harman, 1982; Tegner, 1985; Fregert and Tegner, 1971; Hatch and Maibach, 1986, Scheman et al., 1998; Sommer et al., 1999; BG Chemie, 1995). Many of the examined cases showed patch test results to both CAS No. 1854-26-8 and formaldehyde (a probable contaminant). Because the methylated imidazolidinone used for patch testing was not analyzed in any of the studies, one cannot conclude that the methylated imidazolidinone (and not contaminating formaldehyde) was the sensitizer. Because the methylated material is less likely to release formaldehyde than the nonmethylated material, the potential for sensitization to occur due to formaldehyde exposure is expected to be low.

4.5.6.3 Toxicokinetics

Results of studies in rats and monkeys indicate that non-methylated imidazolidinone (CAS No. 1854-26-8) is poorly absorbed from the skin (Jeffcoat, 1984; 1985). Hydration of the skin increases absorption. After oral or intravenous administration, the material is quickly distributed to the skin, muscle, blood, liver and kidney (Robbins et al., 1984, Robbins and Norred, 1984; Jeffcoat, 1985). Within 24-hours of oral or intravenous administration, the vast majority of the material is excreted unchanged in the urine (Jeffcoat, 1985). Based on the structural similarities between the methylated and nonmethylated material, the methylated imidazolidinone (CAS No. 68411-81-4) is likely to have a similar pharmacokinetic profile as the nonmethylated material.

5. Summary

In summary, based on the structural/physical similarities and chemical physical between methylated imidazolidinone (CAS No. 68411-81-4), dimethylated material (CAS No. 3001-61-4), and non-methylated imidazolidinone (CAS No. 1854-26-8), the data for the non-methylated and/or dimethylated materials are predictive of all endpoints for the methylated material, except for biodegradation and algal toxicity. Studies conforming to OECD Guidelines 301 and 201 were conducted to address these respective endpoints. Sufficient physical/ chemistry data for the actual test material, modeled environmental fate data for the dimethylated material (CAS No. 3001-61-4), biodegradation data for the actual test material, and experimental ecotoxicity and mammalian toxicity data for the methylated and nonmethylated material are now present to satisfy all endpoints (Tables 5 and 6). This test plan is considered final.

Table 5. Test Plan

CAS **No. 68411-81-4**	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
ENDPOINT	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYS/CHEM PROPERTIES							
Melting Point	Y	Y	N	N	Y	Y	N
Boiling Point	Y	Y	N	Y	Y	Y	N
Vapor Pressure	Y[1]	N	N	N	N	N	N
Partition Coefficient	Y	N	Y	N	Y	Y	N
Water Solubility	Y	Y	N	N	Y	Y	N
ENVIRONMENTAL FATE							
Photodegradation	Y*	N	Y	Y	N	Y	N
Stability in Water	Y[2]	N	N	N	N	N	N
Biodegradation	Y	Y	N	N	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y*	N	Y	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y*	N	Y	N	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y*	N	Y	N	N	Y	N
Toxicity to Aquatic Plants	Y	Y	N	N	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y*	N	Y	N	N	N	N
Repeated Dose Toxicity	Y*	N	Y	N	N	Y	N
Genetic Toxicity-Mutation	Y*	N	Y	N	N	N	N
Genetic Toxicity-Chromosomal Aberrations (mouse micronucleus)	Y*	Y	N	N	Y	Y	N
Toxicity to Reproduction	Y*	N	Y	N	N	Y	N
Developmental Toxicity	Y*	Y	N	N	Y	Y	N
OTHER TOXICITY DATA							
Skin Irritation	Y*	N	Y	N	N	Y	N
Eye Irritation	Y*	N	Y	N	N	Y	N
Skin Sensitization	Y*	N	Y	N	N	Y	N
Absorption	Y*	N	Y	N	N	Y	N

*Data on surrogate chemical (CAS No. 1854-26-8) are used

[1] Actual value is not known; however is likely to be close to that of water, since the product is commercially available as an aqueous concentrate.

[2] Actual value is not known; however material is likely to be stable in water because it is sold in the form of an aqueous concentrate.

Table 6. Analog Matrix for 2-Imidazolidinone, 4,5-dihydroxy-1,3-bis(hydroxymethyl)-, methylated*

ENDPOINT	68411-81-4 (Methylated) (Test substance)	1854-26-8 (Non-methylated) (Analog)	3001-61-4 (Dimethylated) (Analog)
PHYSICAL CHEMISTRY			
Melting point	A	A	NR
Boiling point	A	A	NR
Density	A	A	NR
Vapor Pressure	E	E	NR
Water Solubility	A	A	NR
Kow	A	A	NR
ENVIRONMENTAL FATE			
Photodegradation	R	Calc.	Calc.
Stability in Water	E	E	NR
Biodegradation	A	NR	NR
Transport between Environmental Compartments (Fugacity)	R	Calc.	Calc.
ECOTOXICITY			
Acute Toxicity to Fish	R	A & Calc.	Calc.
Acute Toxicity to Aquatic Invertebrates	R	A & Calc.	Calc.
Toxicity to Aquatic Plants	A	A & Calc.	Calc.
TOXICOLOGICAL DATA			
Acute Toxicity	R	A	NR
Repeated Dose Toxicity	R	A	NR
Genetic Toxicity-Mutation	R	A	NR
Genetic Toxicity-Chromosomal Aberrations	R	A	NR
Carcinogenicity (NR)	NR	NR	NR
Toxicity to Reproduction	R	A	NR
Developmental Toxicity	R	A	NR
OTHER TOXICITY DATA			
Skin Irritation (NR)	R	A	NR
Eye Irritation (NR)	R	A	NR
Skin Sensitization (NR)	R	A	NR
Toxicokinetics (NR)	R	A	NR

* Data on analogs CAS No. 1854-26-8 and 3001-61-4 are shown for comparison.
R = Required endpoint fulfilled by surrogate, SAR; Test = Testing planned to fulfill requirement; Calc. = Calculated value; E = estimated qualitatively; A = Adequate existing data; NR = Not required

6. References

Andersen KE, Hamann K. 1982. Cost benefit of patch testing with textile finish resins. Contact Dermatitis 8:64-67.

BASF AG, Department of Toxicology. 1973. Unpublished study (XXII/230), 23.01.73

BASF AG, Laboratory of Ecology. 1980a. Unpublished data, (Fixapret CP; 28.08.80)

BASF AG, Laboratory of Ecology. 1988. Unpublished data, (1200/87)

BASF AG, Department of Toxicology. 1990. Unpublished study (89/183), 15.05.90

BASF. 1996c. Study No. 96/0117/08/1

BASF AG, Laboratory of Ecology. 1999. Unpublished data (98/0419/51/3), 02.02.1999

BG Chemie. 1995. Dimethyloldihydroxyethylenharnstoff; No. 230, Toxikologische Bewertung, Berufsgenossenscaft der chemischen Industrie, Heidelberg.

BIOPHARM. 1995. Unpublished results, report No. 022 TOX94, June 2, 1995. Sponsored by BG Chemie, Germany

CCR (Cytotest Cell Research GmbH & CoKG). 1992. Unpublished report CCR no. 291407, ZHT Proj. No. 40MO502/919014 (sponsored by BASF AG, Germany, Nov. 10, 1992).

Foureman P, Mason JM, Valencia R, Zimmering S. 1994. Chemical mutagenesis testing in Drosophila. IX. Results of 50 coded compounds tested for the National Toxicology Program. Environ Molec Mutagen 23:51-63.

Fregert S, Tegner E. 1971. Contact Dermatitis News Lett. 9:200.

Hatch KL, Maibach HI. 1986. Textile chemical finish dermatitis. Contact Dermatitis 14:1-13.

HMR (Hoechst Marion Roussel) Deutschland. 1998. Unpublished results, report No. 97.0590, Sept. 25, 1998. Sponsored by BG Chemie, Germany

International Research & Development Corp (IRDC). 1981a. Acute oral toxicity test with dimethylolddihydroxyethylene urea in mice. Unpublished Study Number 5701-301.

International Research & Development Corp (IRDC). 1981b. Acute oral toxicity test with dimethylolddihydroxyethylene urea in rats. Unpublished Study Number 5701-305.

International Research & Development Corp (IRDC). 1981c. Acute inhalation toxicity test with dimethylolddihydroxyethylene urea in mice. Unpublished Study Number 5701-311.

International Research & Development Corp (IRDC). 1981d. Acute inhalation toxicity test with dimethylolddihydroxyethylene urea in rats. Unpublished Study Number 5701-315.

International Research & Development Corp (IRDC). 1981e. Two-week repeated-dose oral toxicity test with dimethylolddihydroxyethylene urea in mice. Unpublished Study Number 5701-302.

International Research & Development Corp (IRDC). 1981f. Two-week repeated-dose oral toxicity test with dimethylolddihydroxyethylene urea in rats. Unpublished Study Number 5701-306.

International Research & Development Corp (IRDC). 1983a. Subchronic oral toxicity test with dimethylolddihydroxyethylene urea in mice. Unpublished Study Number 5701-303.

International Research & Development Corp (IRDC). 1983b. Subchronic oral toxicity test with dimethylolddihydroxyethylene urea in rats. Unpublished Study Number 5701-307.

IUCLID. 2000. Substance ID: 1854-26-8. BASF AG, 04-FEB-2000.

Jeffcoat AR. 1984. Percutaneous penetration of formaldehyde. NTIS/OTS 0512137, Doc ID. 40-8470033

Jeffcoat AR. 1985. Nat. Inst. Environ. Health, Research Triangle Institute, "Adsorption, Disposition, Metabolism and Excretion of 1,3-Dimethylol-4,5-Dihhydroxy-2-imidazolidinone (DMDHEU)", Contract No. N01-ES-1-5007, December 1985

Malten KE. 1964. Textile finish contact hypersensitivity. Arch Dermatol 89:215-221.

Marhold JV (1972 in Czech), cited in RTECS (1999) NIOSH, USA.

MSDS for Freerez® MTH Conc. Document: RZMTHCNC CFLN: AUUS Effective Date: 18 October 2001. Noveon, Inc., 9911 Brecksville Rd., Cleveland, OH 44141-3247.

NTP Annual Plan, Fiscal Year 1984, S. 58

RCC Ltd. Environmental Chemistry & Pharmanalytics. 2004a. Ready biodegradability of Freerez® MTH-68 resin in a CO2 evolution (modified Sturm) test. Study number 852789, dated July 16, 2004, with amendment dated Oct. 14, 2004.

RCC Ltd. Environmental Chemistry & Pharmanalytics. 2004b. Toxicity of Freerez® MTH-68 resin to Scenedesmus Subspicatus in a 72-hour algal growth inhibition test. Study number 852787, dated Aug. 2, 2004, with amendment dated Oct. 14, 2004.

Robbins JD and Norred WP. 1984. NTIS/OTS0512125, 40-8470042.

Robbins JD, Norred WP, Bathija A, Ulsamer AG. 1984. Bioavailability in rabbits of formaldehyde from durable-press textiles. J Toxicol Environ Health 14:453-463.

SIAR for CAS no. 1854-26-8. (Reviewed at SIAM 10)

Scheman AJ, Carroll PA, Brown KH, Osburn AH. 1998. Formaldehyde-related textile allergy: an update. Contact Dermatitis 38:332-336.

Sommer S, Wilkinson SM, Dodman B. 1999. Contact dermatitis due to urea-formaldehyde resin in shin pads. Contact Dermatitis 40:159-160.

Tegner E. 1985. Acta Derm Venereol. (Stockholm). 65:254-257.

Tognucci A. 2001a."Determination of the Freezing Point/Freezing Range of Freerez® MTH Conc," Study No. 822690, RCC Ltd 4452 Itingen Switzerland.

Tognucci A. 2001b. "Determination of the Boiling Point/Boiling Range of Freerez® MTH Concentrate," Study No. 822701, RCC Ltd, 4452 Itingen, Switzerland.

Tognucci A, 2001c. "Determination of the Partition Coefficient (N-Octanol/Water) of Freerez® MTH Concentrate," Study No. 882723, RCC Ltd, 4452 Itingen, Switzerland.

Tognucci A. 2001d. "Determination of the Water Solubility of Freerez® MTH Concentrate," Study No. 822712, RCC Ltd, 4452 Itingen, Switzerland.

Zeiger E, Anderson B, Haworth S et al. 1987. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ Mutagen 9(Suppl. 9):1-110.

7. Appendix 1- IUCLID Data Set with Robust Summaries